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EDITORIAL

On these pages the editor offers his opinions, unshackled by advertising patrons and unrestrained by anything save a sense of the decent and the truthful—the editor, alone, is responsible for their type, their tone and their tenor.

WHAT IS TRUTH?

"WHAT is Truth," said Pilate, that unwitting instrument of the greatest plan ever conceived for the redemption of the sub-angelic sons of Adam.

Adam, himself, we must remember, had an inquiring mind. He was something of a researcher; hence the apple episode—and the forthwith transfer of the primal pair, to Eden suburbs, with leaving to us, their children, a legacy of sin and sweat.

And from Adam, through Pilate, to Einstein, answers to the eternal question have been always unconvincing.

More than likely this self same question will be the last vain mouthing of the last lone son of Adam, when he disappears through the portal of the world's last sunset into the endlessness of time. In the meantime, however, we do our share who even vainly search for truth and though a million old beliefs are ruined by such a search we still search on. And time itself is Truth's most helpful friend.

But it has come to pass in these latter days that truth is less revealed than ever, not of its own inherent essence, but because of a purposeful, propagandist, concealment of it.

"It has always been the subtlety of grand deceivers, to graft their greatest errors on some material truths, thus to make them pass unnoticed by those who look more at the root than at the fruit."

I am particularly thinking of the naivete of some, who even in the pursuit of the professions gain their biased ends by stretching a half-truth or less, to the apparent coverage of a full-fledged truth.

And even in the literature of science are those who rush to print, with truth-veneered persiflage, the work of alleged scientific authors and researchers who, in fact, are but pawns of propaganda purveyors.

The discriminating reader is often at a loss to know how trustworthy a record of research may be, when he suspects that it may have been sponsored by someone more eager to sell than to show, or by someone over eager to convince. That most of the recent scientific

studies of milk were subsidized by the large milk product dealers, and must accordingly favor their product, flavors the whole scheme with bias.

A certain laxative, nationally popularized, earned the ill-will of the all-high in the medical field, until a well-heeled organization, promoting the stuff, generously financed a so-called research, and established "beyond doubt" the relative harmlessness of the drug "in medicinal doses." *O Tempora—O Mores!* Directed research is splendid if it is honestly directed,—provided that in stating the half-truth it also tells what the other half represents. But research that seeks only the biased result is worse than no research at all. Hasten the day when we can again place the needed confidence in the integrity of scientific writings, when we can again be convinced that workers in science will let the mess of pottage pass and take instead, their birthright.

"Truth can hardly be expected to adapt herself to the crooked policy and wily sinuosities of worldly affairs; for Truth, like light, travels only in straight lines."

So said Colton—as a partial answer to Pilate!

IVOR GRIFFITH.

Propadrine Hydrochloride Accepted for Admission to N. N. R. Report of Council on Pharmacy and Chemistry, *J. A. M. A. 109,* 16 (1937). Propadrine hydrochloride, the monohydrochloride of a base resembling ephedrine, differing in that the methyl group on the amino group is replaced by a hydrogen atom has been accepted for admission in the N. N. R. Its action is said to be somewhat more prolonged than that of ephedrine, whose action it resembles; also the anxiety complex is not so apt to ensue as with ephedrine. Used locally in 1 per cent. aqueous solution and 0.66 per cent. jelly and orally in ⅜ grain doses every two to four hours, no toxic effects have been noted but continued overdosage should be avoided, as with other vasoconstrictors. H. P. F.

ORIGINAL ARTICLES

NEW FOOD LEGISLATION IN PENNSYLVANIA*

By Elmer E. Harter, Jr., Director, Bureau of Foods and Chemistry

As evidenced by this informative and authoritative article, Pennsylvania's food legislation marches on; and without waiting for the slower, although certain, Federal Legislation of a similar order.

DURING the past session of the General Assembly of Pennsylvania the Department of Agriculture inaugurated and successfully sponsored a legislature program consisting of nine bills relating to food regulation. All nine bills have been enacted into legislation and are now in effect. It is now felt that Pennsylvania has made drastic progressive advances in food control.

Heretofore our practice permitted action only against individuals in the case of adulterated food unfit for human consumption. While this penalized the individual responsible it did not prevent such foods from reaching the consuming public. Thus while our action had some deterrent value we could not adequately perform our task of protecting the public health. Legislatures have always been opposed to the placing of too much power in administrative bodies. They have always been opposed to intrusting to administrative discretion the power to seize, but the legislature of Pennsylvania has been convinced by the Department of Agriculture that the solution to the problem is in the choice of responsible administrative officials, and that in a field so important as food law enforcement the power to seize is the most effective weapon that can be used in the protection of the public health.

Now Pennsylvania possesses the power to enter into any place where food is produced, manufactured, sold or offered for sale or kept, and to seize all articles of food produced, manufactured, sold, offered for sale or kept in violation of the food laws of Pennsylvania. This confers upon the Department unlimited power in this respect.

*Delivered before the Quarterly Meeting of the Philadelphia Conference of Municipal, State and Federal Dairy, Drug and Health Officials, New Customs House, Philadelphia, October 8, 1937.

The Department of Justice is now engaged upon working out a method of procedure for carrying this power into effect.

Heretofore the Department possessed the right to adopt definitions of and standards for food products but the possession of this power was somewhat in doubt. However, it was clear that, if such a power was possessed, it was incumbent upon the Department to adopt as a definition of and a standard for a food product the practice prevalent among the trade. The legislature realized the fallaciousness of this position and has now given us the power to adopt such definitions and standards without regard to the practices of the trade. This in itself constitutes a tremendous stride forward. As a companionate power the Department of Justice now possesses the right of enjoining repeated violations of the food laws, a power which was not heretofore possessed.

The right to proceed against the individual by imposition of fines and confinement to jail in certain cases still remains. Thus the Department possesses a four-way threat against violators of the food laws.

Heretofore violation of our laws were designated misdemeanors and prosecution therefor originated before the minor judiciary who had the power solely to discharge the defendant for lack of evidence or bind him over for the next term of criminal court when a prima facie case was made out against him. This deprived our laws of a great deal of their effectiveness for, because of congested dockets in our courts, it was sometimes a year or more before a defendant could be brought before the bar of justice. Thus a defendant could palm off upon the consuming public a misbranded or deleterious article of food, and the most that could happen to him was another arrest, charged with a misdemeanor. In the meanwhile, pending the trial of his case, he could continue to distribute such food to the public and our only weapon against the continued sale of such food was continued arrests. This practice in some instances proved of little deterrent value in the case of those who were making tremendous illegal profits and who valued little their reputation.

In order to obtain speeedier and more effective action, offenses were changed from misdemeanors to summary ones, giving the minor judiciary the right to impose sentence and allowing the defendant the right to petition the courts for leave to appeal, providing such petition was presented to the courts within five days after the imposition of

sentence by the hearing magistrate. It can be readily seen that this results in speedier and more effective action. When such appeals are permitted by the courts, cases are heard de novo without trial by jury, thus eliminating the sympathies and prejudices of juries which have sometimes wreaked havoc in food law prosecutions.

So the law of Pennsylvania now is, in the great majority of cases, that a defendant may be summarily sentenced on his first two violations and third and subsequent offenses remain misdemeanors, but in all cases more drastic penalties with alternative jail sentences accompany conviction of said offenses.

In addition to this quicker and more effective method the Department can exercise the powers enumerated earlier, to wit: seizure of the food products and enjoining of the offense.

Supplementing these broad unlimited powers it is now unlawful in Pennsylvania for any person manufacturing articles of food or selling articles of food whether at wholesale or retail to have in his possession or transport any articles of food which are adulterated unless the same has been completely denatured and rendered unfit for food by kerosene or other suitable denaturant prescribed by the Department of Agriculture.

I have tried to state to you in a concise manner the most drastic changes in the food laws of our Commonwealth, but there are numerous other changes which will be of interest.

We now have three new labeling laws which are the subject of much discussion among the trade. The Department was of the opinion and still is that every food product should contain upon its wrapping or container a statement of its origin, to wit: the name and address of the manufacturer or packer thereof. The reason for this is obvious. This would first permit the agents of the Department to supervise the conditions under which food products are prepared and thus prevent contamination and unwholesomeness. Second, if contamination and unwholesomeness should result, agents of the Department would know exactly where to go to prevent further contamination and unwholesomeness. However, we were not entirely successful in maintaining this position. The legislature has provided two alternatives in the labeling of food products. First, every package must contain the name and address of the manufacturer or packer thereof preceded by the words "manufactured by" or "packed by" or followed by the words "manufacturer" or "packer".

In lieu thereof the package may contain the name of the distributor or wholesale dealer preceded by the words "distributed by" or "packed for" or followed by the words "distributor" or "wholesale dealer". In this latter alternative the package must also contain a code marking which will identify to the wholesale dealer or distributor the name and address of the actual manufacturer or packer and records of such code marking must be kept by the distributor and wholesale dealer for a period of five years from the date of the sale of the products by them, and such records must be open to the inspection of the Department. Thus, in the one instance the Department can tell by looking at the package where the product originated and in all others it has a quick means of identifying the origin.

This procedure in labeling applies to all food products sold in Pennsylvania except where the legislature has provided a different method of labeling for certain products, and the legislature has done so in the case of carbonated beverages and bakery products.

Under the carbonated beverage and still drink law of Pennsylvania every bottle containing such a beverage must contain the name and address of the actual bottler thereof. No alternative in this classification is provided. However, a distinction is made in the case of fruit juices packed in hermetically sealed cans. In such cases the labeling provisions first mentioned above are applicable.

Under the Bakery Law of Pennsylvania every bakery product which is wrapped must contain thereon either the name of the bakery or the name and address of the distributor preceded by the words "distributed by" or followed by the word "distributor". In this latter instance the requirements for code markings listed above are applicable.

Under the criminal law of Pennsylvania a defendant is presumed to be innocent until his guilt is proved beyond a reasonable doubt, and the burden of proof is upon the Commonwealth. Until this burden is met the defendant is not required to offer a word in his own defense nor can a conviction be sustained. It might be added, in passing, that in no case can a defendant be required to testify in his own behalf. It is obvious that this places a tremendous responsibiltiy upon the prosecution. The legislature came to our rescue to a certain extent and while maintaining the safeguards provided for its citizens, has stated that the possession of any adulterated or misbranded article of food shall be deemed prima facie evidence or an intent to sell such article of food.

Heretofore our law deemed a food product to be adulterated if among other things it was produced, stored, transported or kept in a way or manner that *would* render the article diseased, contaminated or unwholesome. I call your attention to a practice, at one time prevalent in Pennsylvania and in most states, of placing unprotected food products in an unprotected manner on counters in stores where said products were exposed to the dust of the air, handling by prospective customers, coughing, sneezing, etc. This was regarded as a reprehensible practice on the part of food handlers. Upon request scrupulous handlers of food products complied with the requirements that all unwrapped food products be protected from such exposure. Certain individuals contested our requirements and while successive juries convicted defendants on charges of this nature, courts always upset the verdicts deciding that the words *"would* render the article diseased, contaminated or unwholesome" required the Department to prove "absolute certainty" rather than "possibility". As a matter of proof, it was impossible for our experts to prove "absolute certainty". Rather, they could merely express their opinion that such exposure might possibly result in contamination. The courts ruled that this was insufficient. Therefore, this provision of the law has been changed to read that, a food product is contaminated if it is "produced, stored, transported, exposed or kept in a way or manner that *might tend to* render the article diseased, contaminated or unwholesome." Now the law of evidence will be satisfied if our experts say that the article of food may possibly be contaminated by such exposure. A decided improvement has taken place in this respect.

Another important change consists in the following. Heretofore the use of saccharin as an artificial sweetening agent in food products for diabetics was prohibited in Pennsylvania. This required diabetics to use insulin in order to protect their health. I presume that you all have some knowledge of the effects of insulin either from under or over dosages and the difficulty in ascertaining the proper dosage.

Now saccharin is permitted in all food products except carbonated beverages and ice cream, for the prohibition in such laws was allowed to remain. But appropriate warning statements to be prescribed by the Department of Agriculture must be used in connection with the sale of said products. This is believed to be a tremendous stride forward by medical experts and will be of invaluable aid to that large group of unfortunates commonly known as diabetics, and I am in-

formed by medical experts that the use of saccharin sweetened food products will do away with the necessity of the use of insulin to a great degree.

Another important change in the law prohibits the use of artificial color in orangeade or orange drinks where the tendency is to mislead the public by imitating or simulating the appearance of the natural juice of the orange. The particular wording of this section is designed so that the Department may construe it to eliminate any group of beverages having such a tendency and it is now incumbent upon the Department to draw the line of demarcation. This provision of the law was necessitated by the fraudulent practices of certain companies of offering to the unknowing housewife a beverage which purported and was represented to be pure orange juice whereas, as a matter of fact, there was little if any orange juice present therein, for the product was highly flavored and artificially colored to give the appearance of pure orange juice.

Numerous other changes were effected in our laws which, among other things, were designed to protect the Pennsylvania Food industry against out of the State unfair competition. Pennsylvania welcomes fair competition by out of the State food manufacturers and distributors but insists that they be compelled to conform to the same requirements of Pennsylvania in the same business.

Such stringent food control guarantees Pennsylvanians better food than ever before, assures the honest manufacturer and distributor of fair competition and requires the unscrupulous to "take to cover".

Whooping Cough Vaccine. R. T. Lucas, *Tri-State M. J. 9,* 1912 (1937). Of 154 children given prophylactic injections of Sauer's whooping cough vaccine only three were known to develop whooping cough, and in these the symptoms were mild. Pertussis undenatured antigen given to 2 children after exposure to infection failed to develop the disease, even though there was continued intimate contact with a case. Of 15 children given the same antigen therapeutically, 4 showed marked improvement, 8 slight improvement and 3 no improvement. L. G.

CONCERNING THE NATURE OF VITAMIN E

By E. M. Watson, M. D., M. Sc., (West Ont.), F. R. C. P. (Edin.)
Professor of Pathological Chemistry in the University of Western Ontario Medical School, London, Canada;

and

C. S. McArthur, B. A. (West Ont.)
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THE experimental investigations of Evans and Bishop (1922) and Sure (1923) established a relationship between vitamin E and fertility in small animals such as mice and rats. Recent clinical observations suggest that the factor may be useful as a therapeutic agent in combating certain reproductive difficulties affecting human beings. Still more recently, research concerning the chemical and structural nature of vitamin E has progressed to the stage where it seems probable that its true character may be elucidated and its synthetic preparation accomplished.

The fat-soluble vitamin E is known to be present in several natural foods where it exists in the leaves and seeds of plants. The embryo of wheat is especially rich in the factor, consequently wheat germ oil is a valuable source of the vitamin for experimental and therapeutic purposes. Cottonseed oil also contains a plentiful supply of the vitamin.

Clinical Applications

Attention was directed to the therapeutic possibilities of wheat germ oil by Vogt-Möller (1931) who reported the cases of two apparently healthy women, one of whom had experienced four, and the other five, spontaneous abortions, for which no cause could be ascribed. Each of these women during a subsequent pregnancy received wheat germ oil and went through the whole period of gestation successfully and delivered a normal, full-term, living child. In subsequent communications, Vogt-Möller (1933, 1936) presented further observations concerning the clinical use of wheat germ oil and reported that 54 of 71 women with histories of two or more spontaneous abortions continued their pregnancies to a successful termination following the oral administration of the oil.

The experience of other observers has been similar. For example, Juhász-Schäffer (1933) mentioned five cases of habitual abortion where full-term, normal, living infants were born after wheat germ oil had been prescribed to the expectant mothers. McGonigle (1935) observed that 16 women with histories of miscarriages, premature and stillbirths, delivered living children following the use of the oil. Currie (1936) reported 22 living children from 23 subjects of habitual abortion treated with vitamin E alone, or administered in combination with the vitamins A and D.

The series of 80 wheat germ oil-treated cases reported previously by Watson and Tew (1935) and Watson (1936) has been extended to include 120 cases. Of this number, 28 had experienced three or more spontaneous abortions before the institution of wheat germ oil therapy, and all but five of these women gave birth to living children following the ingestion of the oil. Twenty-one of a group of 27 patients, each with a history of two spontaneous abortions, successfully completed their pregnancies with the aid of the treatment. Of 17 individuals with but a single miscarriage, 15 were successful. In 22 out of 30 women who received wheat germ oil for the relief of threatened abortion, the symptoms subsided and the pregnancies proceeded to term. Eighteen non-pregnant, non-fertile women received wheat germ oil with a view to facilitating impregnation but in none of these did pregnancy ensue.

A review of all the available data reveals the attainment of successful results, that is, the delivery of full-term, normal infants, in about 80 per cent. of cases of habitual abortion treated with wheat germ oil. The treatment is of no avail in women with primary sterility.

Pathological Considerations

The clinical observations referred to above point to a relationship between the normal course of gestation in women and something which is present in wheat germ oil. The actual rôle of vitamin E in human reproduction has not been decided but certain inferences may be deduced from the results of experiments with small animals.

Judging from the effects of the deprivation of vitamin E in mice and rats, it appears that this agent is essential for the normal development of the embryo, because in the absence of the specific factor, fœtal growth ceases at a certain stage, gestation comes to an end

and the dead fœtuses are resorbed. It is difficult to formulate an analogy between these resorption gestations in animals and spontaneous abortions in women. Nor is there any apparent association between the occurrence of human abortions and a deficiency of vitamin E. Those who exhibit the phenomenon of repeated spontaneous abortions do not appear to consume less vitamin E in their food than women who do not experience such misfortunes. Perhaps the problem is one of relative dietary deficiency related to individual requirements, utilization, or storage of the vitamin. In this regard it is noteworthy that some observers (e. g. Theobald 1937) maintain that nutritional factors are of greater importance in the conservation of normal pregnancy than is generally realized.

Physiological Aspects

As mentioned above, the means by which vitamin E exerts its influence has not yet been explained. It is not known whether it acts directly upon the embryo or the placenta, or whether it affects these structures indirectly by contributing to the formation or the functional activity of one or other of the hormones.

Considerable research has been undertaken in an attempt to establish a relationship between vitamin E and the endocrine system but the results reported by various workers are rather controversial. It is generally agreed, however, that no degenerative changes occur in the ovaries of vitamin E-deficient rats. No oestrogenic effect is produced by wheat germ oil in castrated adult female rats, as shown by Saphir (1936), who, also, was unable to demonstrate any luteinizing action of the oil in infantile rats following the injection of a follicle-stimulating extract. Shute (1936) postulates the existence of a balance between vitamin E and oestrin, or an oestrin-like substance, in the blood during pregnancy and he maintains that vitamin E exerts a controlling influence upon this hormone, preventing its undue activity or accumulation in excessive amount in the blood.

Despite the fact that the administration of an extract of the anterior lobe of the pituitary will not prevent fœtal resorption in E-deficient animals, the observations of Rowlands and Singer (1936) suggest that vitamin E may be a factor in the elaboration of gonadotropic material by the anterior pituitary body. The experiments of Barrie (1937) led to the conclusion that in the rat, vitamin E is necessary for the normal functions of the anterior lobe of the pituitary

gland and that it contributes to the secretion of the various hormones elaborated by this organ.

Nielsen (quoted by Vogt-Möller 1936) suggests that vitamin E takes part in the synthesis of the corpus luteum hormone which is essential for the nidation and the early stages of development of the fertilized ovum in the uterus. Apropos of this remark, it is noteworthy that the therapeutic effects of wheat germ oil and progestin in habitual and threatened abortions are quite similar. Falls, Lackner and Krohn (1936) recorded in the neighborhood of 80 per cent. successful results in the treatment of habitual abortion with progestin, which happens to be the figure mentioned above in connection with the results of the treatment of the same disorder with wheat germ oil. Until more definite knowledge pertaining to the relationship of vitamin E and the corpus luteum hormone is available, it is unwarranted to assume that the one may substitute for the other therapeutically.

The Chemistry of Vitamin E

During their early attempts to concentrate vitamin E, Sure (1926) and Evans and Burr (1927) demonstrated that the factor was present in the non-saponifiable portion of wheat germ oil. While numerous endeavors have been made subsequently to isolate the vitamin (Olcott 1934, Olcott and Mattill 1931, 1934) the most successful were those of Evans, Emerson and Emerson (1936) who prepared allophanates from the sterol-free, non-saponifiable material derived from wheat germ oil and separated these by fractional crystallization. Olcott (1935) had demonstrated previously the alcoholic nature of vitamin E, and Evans, Emerson and Emerson (1936) obtained from their allophanates alcohols which exhibited the biological properties of the vitamin. The one which showed the most pronounced vitamin E-like effect they named α-tocopherol and ascribed to it the provisional formula $C_{29}H_{50}O_2$, without suggesting any molecular configuration.

Drummond, Singer and MacWalter (1935) suggested that vitamin E was an unsaturated compound probably related to the sterols. Askew (1935), as a result of the study of monomolecular films of vitamin E concentrates, concluded that, if the vitamin molecule contained more than one polar group, these must be adjacent and situated at one end of the molecule. His observations indicated, also, that vitamin E possessed, perhaps, a cyclic structure.

McArthur and Watson (1937) reported the isolation of duroquinone as a result of the selenium dehydrogenation of α-tocopherol and inferred that the duroquinone represented a side-chain containing the two oxygen atoms of the α-tocopherol molecule. Fernholz (1937) and Todd *et al.* (1937) obtained durohydroquinone as a product of the thermal decomposition of α-tocopherol.

The results of these experiments, together with information relating to the antioxygenic properties of the tocopherols (Olcott and Emerson 1937), support the view, as proposed by Fernholz (1937), that the tocopherols are mono-ethers of durohydroquinone.

Thus the preliminary steps in the elucidation of the chemical nature of vitamin E have been made. Further work is in progress in an attempt to determine its molecular configuration. Furthermore, synthesis of the vitamin is anticipated.

We wish to express our thanks to Messrs. Mead, Johnson and Company for a grant-in-aid of our work; also, to the Canada Pharmacal Company for their generosity in supplying wheat germ oil; to Professor W. P. Tew of the Department of Obstetrics for his interest and encouragement throughout the investigations; and to the many practitioners who co-operated by supplying clinical data.

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A Comparative Study of Oral and Subcutaneous Vaccination Against Typhoid Fever Based on Agglutination Titrations. H. D. Moor and I. L. Brown, *J. Lab. Clin. Med. 22,* 1216 (1937). Subcutaneous and oral immunization against typhoid fever were compared on a basis of agglutination titrations performed 4 weeks after vaccination. Three injections were given at weekly intervals, of 0.5, 1.0 and 1.0 cc. of triple vaccine consisting of 1,100 million bacilli per cc. and 500 million per cc. each of paratyphoid A and B bacilli per cc. suspended in saline, heat killed and preserved with Merthiolate. The oral administration consisted in giving, on each of 3 consecutive mornings, 1 gelatin capsule containing 10 billion heat-killed typhoid bacilli per cc. The capsules were given 1 hour before breakfast. The first of the 3 was taken 15 minutes after taking a capsule of bile. 107 people were vaccinated by the oral route and 80 by the subcutaneous method. The agglutinin content was as great or greater after the oral administration as after the subcutaneous method. No reactions with the exception of some nausea in 3 cases were observed in the groups receiving oral vaccination, whereas there was the usual local reactions in all and general systemic observations in 50 per cent. of those vaccinated by the subcutaneous method. Oral administration therefore appears more advantageous. L. G.

NEW WATER SOLUBLE THEOPHYLLINE COMPOUND*

By Frederick R. Greenbaum, D. Sc.**

OUR interest in water soluble theophylline preparations began when the German product "Euphylline," now called "Metaphylline," was imported to this country and at that time was the only source of a water-soluble theophylline preparation.

"Euphylline" or "Metaphylline," consists of theophylline and ethylenediamine. This combination contains about 75 per cent. of theophylline. The writer succeeded in 1930 in preparing theophylline ethylenediamine and its clinical application stimulated my interest in developing similar water soluble theophylline products.

Shonle (1) succeeded in combining theophylline with monoethanolamine and tri-ethanolamine. Kohlstadt (2) described in 1932 the preparation of theophylline with di-ethanolamine.

In our Research Laboratories, we first tried combinations of theophylline with the bases morpholine, propylenediamine and ethylamine in mono-molecular proportions, also, theophylline with these bases in "di" and tri-molecular proportions were tried. These compounds did not possess sufficient solubility in water to warrant further study. We then combined theophylline with piperidine and with triethylenetriamine in "mono" or polymolecular proportions. However, such combinations are only slightly soluble and unstable.

It was not until piperazine hydrate was used that we succeeded in obtaining a combination of theophylline that proved of interest from the point of solubility. Theophylline forms very soluble salts with piperazine, especially the "di" and tri-piperazine salts. The monopiperazine theophylline is soluble to about 6 per cent., while the dipiperazine and tri-piperazine combination form solutions easily up to 40 per cent. As a matter of illustration, 198 grams of theophylline are suspended in about 500 cc. of water. Then, 208 grams of piperazine hydrate are added. Upon stirring and gentle warming to about 50-60° C. the theophylline goes into solution as the dipiperazine theophylline. The volume is then brought to 1000 cc.

It is interesting to note that Aminophyllin is the theophylline ethylenediamine combination. Piperazine is di-ethylenediamine and

*Presented before the Medicinal Division of the American Chemical Society, April 15, 1937, Chapel Hill, North Carolina.

**From the Research Laboratories of The National Drug Company.

forms a definite compound with theophylline. On studying the literature we learned this compound was patented by Gruter (3) in 1909. The same patent covers the combination of theophylline with ethylenediamine.

It is strange that while theophylline ethylenediamine is utilized extensively, theophylline piperazine or theophylline di-ethylenediamine was apparently never tried clinically. At least, we have not been able to find a clinical report. For this reason we decided to study the physiological piperazine theophylline on animals.

When theophylline piperazine solutions are freshly prepared we can give up to 0.5 cc. of 35 per cent. di-piperazine theophylline intravaneously to rabbits and 2.5 cc. intramuscularly. The dilute solution containing 2.75 per cent. of mono-piperazine theophylline could be given intravenously to rabbits in a dose of 10 cc. A marked diuresis occurred after the injections of fresh solutions.

If, however, the 35 per cent. and 2.75 per cent. piperazine theophylline solutions were allowed to stand for a period of 6-8 weeks, the following results were obtained.

Results with Di-piperazine Theophylline

The studies on the 35 per cent. solution of dipiperazine theophylline were started with an oral dose of 1 cc. daily. This gave rise to marked cardiac and respiratory disturbances in a few minutes and during the next two hours there was definite rise in the temperature the first day, but a slight fall in temperature following the second and third doses. During the ensuing twenty-four hours the urinary output decreased.

The rabbit was given one-half cc. dose the next day but all the symptoms were more severe than before. There appears to be a cumulative effect. The animal died during the week-end. No autopsy possible.

Another rabbit was given one-quarter cc. of the solution. The symptoms in this rabbit ran about the same course as in the first rabbit. The animal died over the week-end. No autopsy.

Results with Mono-piperazine Theophylline

In the next experiment with mono-piperazine theophylline was made with 2.0 cc. dose daily. The first and second doses caused a

slight rise in temperature and a slight fall on the third day. There was a marked drop in urinary output.

The next week this rabbit was continued under test but the doses were reduced to one-half cc. daily. There was a slight rise in temperature each day and a decided drop in urinary output.

The third week the dose was reduced to one-quarter cc. daily and this dose had no marked influence on the temperature, but about the same effect on the urinary output during the previous two weeks. During the day following the second dose the animal became cyanotic and gasped for breath.

This rabbit was dead the following morning and on autopsy marked congestion of the lungs, liver, spleen and kidneys was evidenced. The heart was somewhat enlarged. The stomach was distended with gas, but no abnormality was noted in the intestines.

The oral route of administration was chosen because this is the route most likely to be used in human beings.

Both preparations in the doses given produced severe cardiac and respiratory distress and both preparations showed accumulative effect in their reactions.

Both preparations had undergone chemical change, as in the later experiments marked infiltration, followed by necrosis, developed. The infiltrations occurred soon after the injections, while necrosis developed by the next day and increased from day to day, as will be seen from the abstracts of the protocols. Neither preparation has, so far, induced definite changes in the temperature of the rabbits.

These experiments showed the preparations to be unstable. In the first series there was some evidence of diuresis, but in the later series we noted the opposite effect, since there was a definite decrease in the daily urinary output, nor was there a return to a normal urinary output in rabbits subjected to several series of injections.

We believe these preparations are not safe for use in human beings unless a definite way may be found of stabilizing them.

This work perhaps explains the fact that while the German patent (3) covers the theophylline ethylenediamine combination, and the theophylline piperazine (or di-ethylenediamine combination) the drug was never utilized clinically because on standing the solution decomposes and forms apparently highly toxic products.

The search for a suitable combination therefore continued. In September, 1936, in visiting the Mellon Institute, during the recent

meeting of the American Chemical Society, I became interested in a development of Dr. H. F. Robertson, who holds a fellowship of the Carbon and Carbide Chemicals Corporation and who had developed some new organic bases, such as mono-isopropanolamine, di-isopropanolamine and tri-isopropanolamine. Through the courtesy of Dr. Robertson, samples of these three bases were supplied to us. We found the di- and tri-isopropanolamine combine with theophylline; but mono-isopropanolamine forms a stable compound. This combination is obtained by adding 198 grams of theophylline to 600 cc. of water and 75 grams of mono-isopropanolamine. Upon stirring and gentle heating a clear solution was obtained, then the volume was brought to 1000 cc. The solution so prepared contained 18 per cent. of the theophylline alkaloid. Of course, instead of water, alcohol may be used and the theophylline and isopropanolamine in the proportions described above. Upon evaporation of the alcohol in vacuo, crystals of the theophylline isopropanolamine were obtained. This salt crystallizes in long prisms and is readily soluble in water. It is a very alkaline salt—when dissolved in water the pH was found to be 9.20. The pH of Aminophyllin solution is also 9.20.

The chemical configuration of the theophylline isopropanolamine would be like this:

$$C_7H_7N_4O_2CH_3\overset{OH}{C}H.CH_2NH_2$$

Animal experiments were then carried out with theophylline isopropanolamine and it was compared to Aminophyllin in its behavior.

Theophylline isopropanolamine produces slight necrosis in rabbits when injected intracutaneously in a dose of 0.1 cc. Intramuscularly a 1 cc. dose causes slight infiltration with heat. Intravenously 7 cc. is less than the maximum tolerating dose.

The hemolytic action of the undiluted theophylline isopropanolamine is slightly greater than that of Aminophyllin.

The two products show no diuretic action on rabbits when compared with the urinary output of a normal rabbit.

These animal experiments have convinced us that theophylline isopropanolamine to which we have given the name "Theopropanol" is of low toxicity, and possesses primarily the therapeutic action of theophylline. Clinical investigations, with theophylline isopropanolamine are now in progress.

Summary

1. A brief outline of water soluble organic theophylline compounds so far known is given.

2. Aminophyllin, theophylline ethylenediamine, has become an accepted U. S. P. Product.

3. Our attempts to prepare a combination of theophylline with other bases are described, particularly with piperazine. This, however, was unstable and upon standing formed toxic products as shown by animal experiments.

4. The development of theophylline isopropanolamine, a new theophylline compound, is described and this preliminary report is herewith presented.

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(2) Koehlstaedt, D. R.: Patent No. 583,054 Kl. 12, Group 7, August 28, 1935.

(3) Gruter, Reinholdt: Assigned to Byk Gulden Werke, Charlottenburg, Germany. Theophylline Compound. U. S. Patent 919,161, April 20, 1909.

Active Immunization of Tuberculous Children Against Whooping Cough with Sauer's Vaccine. M. Siegel and E. W. Goldberger, *J. A. M. A. 109,* 1088 (1937). Sauer's authorized commercial vaccine in doses of 80 billion bacilli, did not seem to prevent the development of symptoms in a group of vaccinated tuberculous children exposed to whooping cough, at Sea View Hospital. The symptoms of the disease, however, appeared to be milder and of shorter duration among the vaccinated than among the non-vaccinated children employed as controls. L. G.

Pertussis Endotoxin in the Treatment of Whooping Cough. A. R. Thompson, *Lancet 233,* 733 (1937). H. pertussis endotoxin in 124 out of 372 hospitalized whooping cough cases appeared to be of value before the onset of whooping cough but not thereafter.

L. G.

ABSTRACTS FROM AND REVIEWS OF THE LITERATURE OF THE SCIENCES SUPPORTING PUBLIC HEALTH

Bacteriology . . . . Louis Gershenfeld, B. Sc., Ph M.
Biochemistry, Nutrition, etc. . . . Arno Viehoever, Ph. D.
Biology . . . . . Marin S. Dunn, Ph. D.
Chemistry . . . . . Arthur Osol, Ph. D.
Pharmacy . . . . . E. Fullerton Cook, Ph. M.
and their assistants

OUTLOOK FOR AN INTERNATIONAL PHARMACOPOEIA

By Dr. L. van Itallie—Leyden*
(Translation by Dr. Arno Viehoever)

The problem of an International Pharmacopœia is not a new one as it had already been discussed 60 years ago, during the First International Congress in Brunswick, Germany. Since then the unification of a pharmacopœia on a smaller or larger scale has been discussed by representatives of pharmacy whenever assembled in an International Conference. As I shall attempt to further the project of an International Pharmacopœia in a practical way I may be permitted to discuss it anew.

Briefly referring to personal previous expressions, may I recall that I discussed the history of International Pharmacopœia problems about 25 years ago during the Eleventh International Congress for Pharmacy. I mentioned then that commissions appointed to give some attention to this problem did not achieve practical results, though the initially purely theoretical idea assumed now more substantial form. It was realized that the plan of a broadly planned International Pharmacopœia might encounter such difficulties as to get nowhere. Thus, only in the limitation of scope could progress be expected.

The congress of 1893, held in Chicago, appointed a commission to arrive at an International agreement concerning potent medicines. Six years later Dr. Rommelaere proposed in the Belgian Academy

*Address before the Tenth General Session of the International Pharmaceutical Federation at Copenhagen, Denmark, August 27, 1937.

of Medicine that the Belgian Government should make contacts with other governments leading to work on an International Pharmacopœia. This proposition was adopted by the Academy limiting the regulation to extremely potent drugs.

We must be grateful that the Belgian Government as a consequence of this decision and of inviting various governments has furthered to a high degree the chance for an agreement.

When the delegates from all European countries and from different other countries assembled in September 1902 in Brussels, they were conscious that much good could be done, even though often with the sacrifice of their own points of view and suppression of National sensibilities. With pride and gratification I can say that in the final session of this conference a preliminary agreement was signed which fixed the composition of a number of highly active medicines.

With few exceptions the agreement has found acceptance in different pharmacopœias, very much to the furtherance of the unification of a number of important medicines. Thus it was no longer possible that in these medications in neighboring countries differences in the content of active substances occurred, which differences in certain cases had assumed serious forms.

Before the Brussels agreement the syrup of iron iodide contained in one country 5 per cent., in a neighboring one 20 per cent. iron iodide. This single example shows the dangers, e. g., in a foreign bathing resort, that were connected with the preparation of a prescription if the medicinal formula of the homeland was not maintained. Many complaints were made. Taste, appearance and action of medicaments were different. Only if the pharmacist is sufficiently orientated and knows different pharmacopœias, disagreeable consequences are avoided.

Only after the decisions of the Brussels convention had received complete consideration in the different pharmacopœias, the differences in the activity was removed.

Much remained to be done. Complete uniformity can only be obtained, if the content in active substances is determined according to the same analytical method. Only through agreement as to the method of preparation can the demand for uniformity in the form of medicines be achieved.

Even during the sessions of the Brussel conference in the year 1902, the desire was expressed to foster, through a permanent Inter-

national secretary, a contact of the commissions, charged with the revision of the pharmacopœia, and thus to arrive at a uniformity of different pharmacopœia.

During the Eleventh International Pharmaceutical Congress in Hague, Netherland, the problem of an International Pharmacopœia was also discussed. It was noted that the desire for the foundation of an International Pharmacopœia secretarial office had not as yet borne fruit. As a result of my proposal, a commission was named which would work out a plan for the organization of this secretarial unit.

The commission was composed of seven members of different pharmacopœial commissions. The report of the commission is to be found on page 92 of Bulletin N:3, 1915; it contained both proposals placed before the commission, one by Prof. Tschirch of Berne, Switzerland, and one by me. While the proposals compared in principle, for the method of procedure my plan was followed.

The unfortunate war made any international effort impossible. The Federation and also many international associations were compelled to largely restrict their efficiency.

In 1922 a general assembly of our Federation took place which, after a short consideration, unanimously accepted the report.

In 1923, in our conference in London, I again brought up the question of the International Pharmacopœia. Among other things I said:

> "In our days because of the increasing traffic between the peoples, the lack of an International Pharmacopœia is an anachronism. The resolutions passed at Brussels have surpassed the average term of life of a pharmacopœia. They need correction on several points and extension in every way."

You will note that I have continually hammered away on that point.

Another request was directed to the Belgium Government to assemble a second conference in order to enlarge the work of the previous conference.

In the session of 1925, I could finally report the good news that a conference had been invited to Brussels. The continued efforts of the Federation were crowned by good results.

In this second Brussels conference resolutions were agreed upon concerning a larger number of highly potent medicines, an inter-

national nomenclature, biological standardization, etc. It was also decided to request from the Hygienic Section of the League of Nations the foundation of a secretarial office for an International Pharmacopœia as well as the appointment of two commissions. One commission would have to be charged with the unification of the chemical and physico-chemical methods for the testing of highly potent medicines, the other with directions for the compounding of galenical preparations.

Although 12 years have passed, these two commissions were not appointed, nor was there organized a secretarial office for International Pharmacopœia by the League of Nations. While the Belgian Pharmacopœia Commission tentatively has taken over the office of an international secretary, as far as I know, confirmation by the League of Nations was never given. It thus appears that the desired agreement between the Belgian Government and the Hygienic Section of the League in Geneva was not obtained.

Our Federation in the meantime has directed its efforts towards an increased promotion of the International Pharmacopœia. The commission appointed in 1927 by the general assembly including besides myself, Eder, Greenish, Schamelhout, Thoms, Tiffenau and von Friederichs offered a report in 1928, defending the desirable and the possible features of an International Pharmacopœia. This report also showed the way to reach the desired aim and contained a basic plan for the work of such International Pharmacopœia Commission. Although almost 10 years have passed since the publication of this report which was sent to the Belgian Government and to the Hygienic Section of the League of Nations, thus far no practical results have been achieved. Even now no agreement has been reached, although, now and then, reports circulate which promise progress.

I believe the Federation will do well to take up the problem anew in its own hands. Our Federation is to be regarded as the highest pharmaceutical parliament, and is entitled to a voice, not comparable to the "voice crying in the wilderness," but loud enough to sound in the ears of the governments concerned.

Hitherto, our Federation has considered only the theoretical phases of the problem. Nevertheless these theoretical considerations have led to a practical plan, which still may form the basis for practical work. We need not defend the reason anew why we desire an International Pharmacopœia. Now we want to see action.

When I come with a special proposition before this assembly, I do not want to be misunderstood.

The Federation must not place itself in the position of the Belgian Government nor that of the League of Nations. To these governing bodies we must leave the fulfillment of the resolutions of the Brussels agreement. Our Federation may well carry out the preliminary labor which would show the practicability of the idea of the International Pharmacopœia. To this preparatory labor a large number of the foremost representatives of pharmacy in the whole world could be called for co-operation and the result of this preliminary labor could serve the respective governments as a guide in their task.

You know, "Everything comes to him who waits." However, we have waited long, and do not see the speedy attainment of the goal. Let us therefore offer a helping hand and pull the plow. The time is ripe. In the International Union of pure and applied chemistry, our colleague, Lormand, secretary of the French Pharmacopœia Commission, has discussed the unification of all pharmaceutically important chemicals, and proposed that the International Union could envision the creation of a commission with the object of unifying the monographs of chemical products listed in the various codices.

With this idea I believe we can all agree. I only would like to see our Federation take over the elaboration of the thought, as already mentioned in the session of the Union in Lucerne.

Some months ago in the *Pharmaceutical Journal,* an appeal was made to leave the decision to an International Pharmacopœia concerning a name to be given to a product called "Ergometrin" in the United States. While I must be brief I must point out the two great advantages of an International Pharmacopœia; first the highly desirable unification of medicines and their preparation as far as galenicals are concerned, and second the testing methods. This would include also economy in labor inasmuch as the pharmacopœia of different countries could immediately utilize the general part elaborated by the International Commission and also utilize the special part after adjusting it to the needs of the respective countries.

I would now propose: The general assembly of the Federation of International Pharmacy decides the appointment of a commission for pharmacopœial work.

The commission, to be considered as the central executive board, is to consist of from seven to nine members, to be chosen from different countries.

The commission has the task of carrying out the preliminary labor for an International Pharmacopœia, following the basic outline given in the report of the commission, 1927-1928. Bulletin de la FIP. p. 11, 1928.

The commission invites a larger number of representatives of scientific and practical pharmacy from different countries to cooperate with them, with the object of transferring subsections of the work mentioned in the above report to smaller commissions of experts called upon for assistance.

The collected reports of this preliminary labor, sent by the commission to the bureau of the Federation, are then to be transmitted to the Belgian Government and the Hygienic Section of the League of Nations.

While I am conscious of the fact that my proposal entails a great amount of work for many of my colleagues, and that financial sacrifices will be demanded from our Federation, I would contrast this with the fact that the good cause will be furthered in large measure, that we shall thereby contribute to the progress of scientific pharmacy, to the peaceful relations between the representatives of different countries, and to the increased prestige which this decision will bring to the Federation of International Pharmacy.

This proposition was accepted.

In the discussion, Dr. Heger, Vienna, referred to his personal attendance in 1885 at the Sixth International Pharmaceutical Congress at Brussels, where the Viennese pharmacist, Anton von Waldheim, as president of the functioning International Pharmacopœia Commission, presented the project of an International Pharmacopœia. This project, published 1885 in the *Pharmazeutische Post,* was then unanimously accepted as a basis for the detailed elaboration of a Pharmacopœia Internationalis. No subsequent action, however, was taken as the Federation of International Pharmacy was not as yet organized.

REPORT ON RHUBARB AND RHAPONTICUM†

By A. Viehoever

(Philadelphia College of Pharmacy and Science, Phila., Pa.), Associate Referee*

In the 1937 Supplement of the U. S. Pharmacopœia, *Rheum rhaponticum* is specifically excluded as an official source of rhubarb.

The chemical tests of identity, representing the so-called Borntraeger color reaction, indicating the presence of emodin and chrysophanic acid, are given by both rhubarb and rhaponticum. Rhaponticin has been found to occur in genuine rhubarb as well as in rhaponticum. No reliable chemical identity tests, nor indeed chemical assay methods, are at present available for the differentiation of rhubarb from rhaponticum and for the evaluation of rhubarb.

The complex chemical composition thus far known has been enumerated in a previous report by this Referee, *This Journal, 16,* 530 (1933). It has also been pointed out in this and other reports,[1] that by using daphnia as a biological test animal a difference has been found in the cathartic effectiveness of both species, rhaponticum having been found weaker than rhubarb. Daphnia for these experiments have been successfully bred in aerated tapwater, containing either 125 mg. of soybean flour (Cellu) and 25 mg. of urea to each gallon, or at most 0.1 per cent. of dried shredded sheep manure,[2] the latter medium usually yielding darker pigmented and thus more conspicuous contents in the food canal.

In order to express the cathartic effectiveness in a definite quantitative way, elaterin has been used as a standard substance. The commercial substance elaterin is a combination of two crystalline compounds: elaterin, α, crystallizing in prisms and melting above 200° C. (230° C. or less), levorotatory, physiologically inactive, not readily soluble in absolute alcohol; and elaterin β, crystallizing in plates melting below 200° C. (190-195° C.(?)), dextrorotatory, readily soluble in absolute alcohol, and physiologically a very active cathartic.

While the complete separation has not been effected, the mixture, upon suspension in culture water, as well as the filtrate of this

† Reprinted from *Jour. A. O. A. C., 20,* 562-564 (1937).

* From the Gross Laboratory for Biological and Biochemical Research.

[1] *J. Am. Pharm. Assoc., 25,* No. 12 (1936).

[2] *Am. J. Pharm., 107,* 103-130 (1935); *109,* 285-316 (1937).

suspension (a fairly coarse filter paper used), has caused speedy evacuation of the entire food canal of daphnia. The speed of complete evacuation, effected generally in 10-20 minutes, markedly exceeded that observed previously for curacao aloe in a concentration of 0.05 per cent.[8]

A tentative assay is suggested for the biological evaluation of rhubarb and rhaponticum, in particular, and for laxative drugs in general. Consideration was given—

I. To the standardization of conditions, as
   1. Number of animals.
   2. Amount of culture water.
   3. Composition including the *p*H [concentration] of the culture water.
   4. Temperature of the culture water.
   5. Pretreatment of the animal (pure line, uniform sex and age).
   6. Manner of administration of the preparation to be tested.

II. Determination of the normality spread of normal deviation, as
   1. The best time interval of observation.
   2. Intensity of effect at a certain prefixed time.

III. Unit of effect (fixed in terms of time and effect).

IV. Variation of reaction of animals.

The Associate Referee will submit the proposed assay method to collaborators. Continuation of the work is recommended.

The method follows:

Assay Method for the Evaluation of Laxatives

Test Object

Daphnia (*Daphnia magna*).—Age 10 days. Reared from pure strains, at temperatures between 68°-72° C. in culture water of known *p*H [concentration] (*p*H 7.8-8.1); female (without eggs or young in the brood sac) from the same colonies, kept under identical conditions and with 100 per cent. filled food canal. Use 30 daphnia for each test.

[8] Viehoever, A., *Am. J. Pharm.*, *107*, 47-72 (1935).

Procedure

Prepare a suspension of reference elaterin (Merck) in concentration of 0.1 gram in 100 cc. of culture water of *p*H 7.8-8.1 and filter through fairly coarse filter paper.[4] Preferably use crystalline elaterin β melting point 197° (?) C., 0.02 gram in 100 cc. of the culture water, and filter. If the solution obtained is to be preserved, check it for potency against freshly prepared solutions at least every month and discard it if not of standard potency.

Add the standard in 0.5 cc. quantities to the test animals, placed singly in special observation "Vic tubes" (flat, 3″ long, 0.5″ wide) freed from decantable culture water.

Observe the speed and extent of evacuation at low magnification (6-10), and check, if desirable, with higher magnification (100). Record the time of approximately 50 per cent. and 100 per cent. evacuations.

To test the preparation, dissolve or suspend it in amounts of 0.1 cc. in 10, 50, and 100 cc. of the same culture water as specified above and filter. Add this test solution in 0.5 cc. quantities to the test animals. Proceed as directed for the standard solution.

Determine the concentration of the test and standard solutions producing the same degree of response.

Diet and Nephritis. Editorial, *J. A. M. A. 109,* 1202 (1937). Laboratory studies on the effect of dietary factors in nephritis have been stimulated by Masugi's recent demonstration that chronic nephritis, closely resembling Bright's disease, can be induced in laboratory animals by the intravenous injection of a properly selected organ-specific nephrotoxic serum. Smadel and Farr of the Rockefeller Institute for Medical Research, by using this method of producing kidney damage and nephritic in rats have studied the result of different diets on the progress of such nephritis. Three different diets were used differing only in the per cent. of protein (lactalbumin) contained. Diet 1 was prepared with 5 per cent. of protein, diet 2 with 18 per cent. protein and diet 3 with 40 per cent. protein.

During the first month the nephritis was identical in all cases. In the second month nephritis symptoms diminished greatly or completely disappeared in all but two of the animals on diet 1. Animals fed on diet 3 developed progressive nephritis and at the end of the

[4] Delta, No. 307, or Amer. Standard, No. 5160.

experimental period only two rats still survived, both of which were in the terminal phase of Bright's disease. Rats fed with diet 2 behaved in a manner intermediate with those on diets 1 and 3. From these results coupled with certain other observations not herein described, Farr and Smadel concluded that "a progressive chronic nephritis may follow a single toxic insult to the kidney" and that "the severity and course of the resulting nephritis is markedly influenced by diet."

L. F. T.

A Technic for the Production of Calcium Gluconate Ampuls. L. Bracaloni, *Bull. Chim. Farmac. 75,* 583 (1936), through *Pharmaz. Zentrh. 78,* 634 (1937). Two hundred grams of calcium gluconate are shaken with 2020 cc. of hot distilled water until dissolved and the solution is then filtered in a covered funnel through a hardened filter. The solution is next sterilized for one-half hour at 112° C., filtered through a sintered glass filter and placed in ampuls. These are, following sealing, again sterilized for one-half hour at 112° C. According to analyses on the sterilized ampuls, no decomposition occurred with the double sterilized product even upon seven months' storage.

L. F. T.

The Use of the Phosphatase Test in Detecting Underpastuerized Milk. J. C. Geiger and C. Davis, *J. A. M. A. 109,* 1363 (1937). The legal standards for the process of pasteurization of milk supplies have been well defined and clarified. Likewise the process is generally accepted as a safety measure particularly in city milk supplies and often in the home. The question as to whether or not a milk has been adequately pasteurized has long been a problem for organizations engaged in dairy control work.

The amylase test is unreliable since it has been found that the amylase content of milk varies so considerably and that it may withstand heating at 65° C. for thirty minutes.

The phosphatase test of Kay and Graham (*J. Dairy Research 6,* No. 2 (1935)) appears to be quite reliable. It is briefly as follows:

1. To 10 cc. of the buffer substrate solution (one tablet containing disodium phenylphosphate and sodium barbitone is dissolved in 50 cc. of water) contained in a 25 cc. stoppered test tube add 0.5 cc. of the milk to be tested and mix thoroughly.

2. Add two drops of chloroform, stopper the tube and incubate at 37-38° C. for one hour.

3. At the end of this time add 4.5 cc. of the diluted Folin and Ciocalteu reagent (1 volume of reagent and 2 volumes of water) mix, allow to stand for three minutes and filter.

4. To 10 cc. of the filtrate add 2 cc. of the sodium carbonate solution (14 per cent. anhydrous sodium carbonate), mix thoroughly and place in boiling water five minutes and again filter.

5. Compare the color of the filtrate in a 13 mm. tube with the Lovibond standard 2.3 blue glass in the "Limitester."

If the color of the filtrate exceeds that of the standard glass it may be safely assumed that the milk has not been properly pasteurized, i. e. the temperature has been too low or the time of heating too short. The method was tested by examining many samples of milk withdrawn at various intervals of the pasteurization treatment. The results indicated the reliability of the method. L. F. T.

A Specification for Toothpaste. W. Souder and Q. C. Schoonover, *J. A. D. A. and D. Cos. 24,* 1817 (1937). The United States Government purchases large quantities of toothpaste for use in its hospitals and similar institutions. The authors as members of the National Bureau of Standards investigated the question of toothpaste characteristics in order to properly draw up specifications for governmental purchase.

Toothpaste was considered from the first as a cosmetic rather than a medicine, since in ordinary practice a medicated paste is not wanted and in those cases wherein a medicated dentifrice is indicated both the formula and its use comes within the scope of either the dentist or the physician.

Formulas for toothpaste are available in many texts. Advertising literature and radio programs spread the claims for unusual virtues of innumerable ingredients which are supposed to be necessary in a first quality toothpaste. A prescription or formula including all these ingredients would be designated by medical experts as a "shot-gun" prescription.

Except in those rare cases of pathologic conditions the toothpaste problem need not become complicated. Safety from injury to oral tissues is the first item to be considered. Next comes the question of efficiency in removing foreign materials from the teeth. Conven-

ience in marketing and using the product also demands attention. Finally comes the question of the final touch of flavor or perfume which is permissible after the teeth have been cleaned. In no case is it wise to substitute this last item for any preceding item.

The foundation for a toothpaste is a powder and plasticizer, one or both of which possess detergent properties. These must not be abrasive to enamel. The compound must be and remain homogeneous. Segregation, fermentation, or hardening during transportation and storage cannot be permitted and the product must not depreciate when subjected to the possible extremes of temperature. Excess acidity or alkalinity and the presence of poisons must be avoided as well as escharotic properties. The authors developed a test for excessive abrasiveness (to be published later) consisting in brief in rubbing the edge of a nickel-copper alloy disc over a soft glass slide for about 100 times with about 5 pounds pressure being exerted, finally washing the slide and examining for scratches. This test will detect, for example, 1 part of emery in 100,000 parts of paste.

No "magic" ingredients are recognized in the specification. Claims for special virtues of an ingredient, if not supported by data beyond a patent, were not accepted. Ingredients having recognized detergent values could not be admitted on these values alone. The possibility of dissolving enamel or producing other types of injury had to be answered by satisfactory laboratory data or by sufficiently prolonged clinical observations. Many popular commercial pastes fail to meet the requirements of composition. The burden of proof that the extra ingredients are really necessary and that they are truly harmless is upon the sponsors of such extra ingredients.

Of twenty-five popular brands of paste in 1936 ten failed to pass the abrasion test, whereas eleven failed to pass other tests. Hardening, segregation and fermentation were the most common faults. Some showed stain or chemical attack on the inner surface of the tube. In one case, small holes, due to corrosion from the paste, appeared in the tube after storage.

Appended to this most interesting paper is Federal Specification FFF-D-191 for Dentifrice which should prove of great value to manufacturers or prospective manufacturers of this commodity as well as all others interested in properly understanding what comprises a safe and sound dentifrice. L. F. T.

Sterilization of Solutions Through Filtration. W. Christiansen. *Pharmaz. Zentrh. 78,* 593 (1937). Medicinal solutions must frequently be sterilized. This is accomplished generally by heating in a steam oven or in an autoclave. In those cases where this kind of sterilization produces undesirable decomposition of the product filtration is employed using the Chamberland, Berkefeld, or some similar type of apparatus.

A short time ago the Jena glass producers, Schott & Gen., Jena developed a new kind of filter that for the rapid sterilization of solutions is particularly good. With this filter there is a cylindrical mantle at the end of which is a short outlet tube. In the bottom of the mantle is fused a double filter plate. The filter can be sterilized as well in an oven as in an autoclave only in order to protect the filter plate it must not be placed while wet into an oven already heated. The purification of the suction filter in order to remove organic matter is accomplished by pouring on the plate some concentrated sulfuric acid warmed to 80° C. and containing either some potassium nitrate or a mixture of sodium nitrate and sodium perchlorate. This is allowed to remain on the plate until the next day, then sucked through and the plate washed with distilled water.

Filtration is accomplished with the following assembly of glass apparatus. In the neck of a sterile suction flask is fastened the filter using a boiled rubber stopper. The suction flask is connected with a three-necked Woulff bottle that has one side connected to a water pump. In the outlet of the suction flask is inserted a sterilized wad of cotton so that when the pressure is released the air rushing into the flask will not carry with it any organisms.

The author conducted several experiments to determine the effectiveness of this new filter in completely sterilizing solutions that were passed through it. Cultures of B. prodigiosus, B. melitensis, B. mesentericus (with spores) and B. fluorescens were added to normal salt solution, the product filtered and the filtrate added both to liquid culture media and on agar plates and then incubated. No growth was found in any case. When the filter was left on the suction flask and the whole incubated for two days at 37° organisms were present in the filtrate due to penetration of plate. Thus it should be remembered that the plate must be initially sterile and that the filtrate should be removed from the suction flask immediately. When small quantities of liquid are passed through such a filter the loss is appreciable amounting to 3-5 cc.

The glass suction filter with the two sintered plates on the basis of this study appears to be very efficient for the sterilization of medicinal solutions. L. F. T.

The Analysis of Aminophylline. F. Reimers, *J. A. O. A. C. 20,* 631 (1937). In presenting methods for the determination of theophylline, ethylene diamine and water in aminophylline the author calls attention to the need of revising the N. N. R. and U. S. P. methods of analysis of the latter compound. To determine theophylline 0.3 gram of aminophylline is dissolved in 2 cc. of water in a small separator; 2 drops of methyl red indicator are added followed by sufficient dilute hydrochloric acid to produce change in color. The mixture is then extracted for 1 minute with 25 cc. of a mixture of 3 volumes of chloroform and 1 volume of isopropyl alcohol, the extract being filtered through a small filter into a weighed flask. The extraction is repeated three times with 20, 20 and 10 cc. respectively, of the same solvent, all the extracts being filtered through the same filter into the flask, the contents of which are then evaporated to dryness on a water bath, finally heated to constant weight at 100° C. as anhydrous theophylline. This method may also be used in determining theophylline in other soluble compounds, such as theophylline-sodium acetate. In this case the acetic acid must be removed by heating with dilute sulfuric acid and water.

From electrometric titrations it was found that ethylene diamine can be titrated accurately as a divalent base if the titration is taken to pH 4.6 with 0.1 N hydrochloric acid. For this purpose bromcresol green functions satisfactorily when titrated to a green color. The titrations are not influenced by the presence of theophylline.

Dried over calcium chloride aminophylline continues to lose weight for 3 days, the decrease being due to loss of water and of ethylene diamine. These two substances can be removed completely by drying at 125° C., therefore, if the drying is carried out in connection with a determination of ethylene diamine it is possible to calculate the amount of water present. The weight of the residue serves as a check on the determination of theophylline. (*Abstractor's note*: Elsewhere in the same journal L. E. Warren, in his report on aminophylline, states that Reimers' procedure, modified to include seven extractions with solvent and evaporation of the residue at 80° C., is the most satisfactory method tried for the determination of theophylline.) A. O.

Rapid Determination of Iron in Pharmaceuticals with the Aid of Cupferron and an Immiscible Solvent. S. M. Berman, J. J. Chap and D. M. Taylor, *J. A. O. A. C. 26,* 635 (1937). A method employing cupferron (the ammonium salt of nitrosophenylhydroxylamine) to precipitate iron followed by extraction of the insoluble compound with chloroform is described. Applied to the determination of iron in twelve common pharmaceutical preparations the method gave results which checked well with results by a standard method. The new method follows: To the solution, placed in a pear-shaped separator and containing not more than 100 mgm. of iron, add sufficient hdyrochloric acid to make the total acidity equivalent to at least 10 cc. of 4-normal acid. Add 6 per cent. aqueous solution of cupferron until the reagent produces a momentarily-white precipitate at the point of contact with the acid solution. Add 10 cc. or more of chloroform and shake the contents of the separator vigorously for 15 seconds. When the layers have separated, again add the reagent until the white precipitate reappears (in the presence of iron the initial white precipitate changes quickly to a pinkish-brown). Repeat the shaking-out process, without removing the chloroform layer, until successive additions of reagent and shaking-out with the immiscible solvent leave a clear aqueous layer. Transfer the chloroform layer to a second separator and extract the aqueous solution in the first separator with small portions of chloroform until the solvent remains colorless, adding the chloroform portions to that in the second separator. Wash the combined chloroform extracts with about 10 cc. of water, transfer the former to a weighed dish suitable for ignition and evaporate the solvent on a steam bath. Heat the residue at 150° to 300° C. under a hood until fuming ceases. Ignite at 500° to 700° C. to constant weight, cool and weigh as Fe_2O_3 or determine the iron volumetrically.

A. O.

The Determination of Small Quantities of Strychnine. A. G. Murray, *J. A. O. A. C. 20,* 638 (1937). The simplicity and accuracy of the titration of iodide with potassium iodate solution suggested to the author the use of the latter in determining the excess of iodide ion in filtrates from strychnine precipitated as the hydriodide-mercuric iodide compound.

Detailed instructions for the assay follow: Dissolve the strychnine in 2 or 3 cc. of dilute sulfuric or hydrochloric acid and transfer

to a 25 cc. graduated flask. Add an accurately measured volume of HgI_2-KI solution (made by dissolving 0.46 gram of HgI_2 and 0.40 gram of KI in water and diluting to 100 cc.), using at least 1 cc. for each 3 mgm. of strychnine. Dilute to the mark. Thoroughly mix the contents of the flask and allow to stand, protected from light, for 1 to 2 hours. Filter, rejecting the first 2 or 3 cc. of filtrate. Transfer 20 cc. of the filtrate to a glass-stoppered bottle. Add about 16 cc. of concentrated hydrochloric acid. Cool, add about 1.5 cc. of chloroform and titrate with standard iodate solution (1.0701 grams of reagent-grade potassium iodate, previously dried at 120° C. in sufficient 1 per cent. hydrochloric acid to make 500 cc.) to a colorless end-point. Carry out a blank determination using the same volume of HgI_2-KI solution. Each cc. of iodate solution is equivalent to 2.228 mgm. of strychnine. Sucrose, lactose, starch and small quantities of nitrates do not influence the determination. Results of the analyses of tablets by this method agree well with results obtained by the N. F. VI procedure. A. O.

Lycopodium Granuloma Resulting from the Use of Anal Suppositories. William Antopol, M. D., and Charles Robbins, M. D., *J. A. M. A. 109*, 15 (1937). In 1933 five cases of lycopodium granuloma were reported. In these instances the spores of lycopodium clavatum—an ingredient of the dusting powder used for surgical gloves—had been introduced into the operative field during the surgical procedure. In 1935 six similar cases in which the spores were also introduced, during operative procedures, were described. Since that time another case of lycopodium granuloma has been reported in which the mode of introduction differed from the previous cases cited. The patient during 1935 had submitted to two operations for external hemorrhoids. No improvement of symptoms and the pain and discharge from the rectum continuing, a fistula in ano was resected two months after the last operation. Microscopic examination showed an acute inflammatory and a chronic granulomatous reaction the composition of which included the spores of lycopodium. Lycopodium had not been used at either hospital where the two operations were performed. Upon questioning it was disclosed the patient had been using, since the first operation, anal suppositories on which lyco-

podium had been used as a dusting powder. When measures were taken to prevent the possibility of reintroduction of the spores the wound healed rapidly and fifteen months after the last operation there has been no recurrence of symptoms. H. P. F.

A Reaction Between Amidopyrine and Aspirin. E. A. Lum, *Pharm. J. 139,* 3854 (1937). The following powder when prepared and allowed to stand for some days was reported to have changed to a yellowish sticky mass, smelling strongly of acetic acid:—

Amidopyrine	6 parts
Aspirin	6 parts
Caffeine citrate	1 part

By elimination it was shown the reactions was due to the mixture of amidopyrine and aspirin. This occurred when the mixture stood in a warm place and was accelerated by using a water bath. At ordinary temperatures a mixture of amidopyrine and aspirin in molecular proportions, allowed to stand for a period of weeks showed no signs of liquefaction but a slight odor of acetic acid developed after one or two weeks. A mixture, in the above proportions, of aspirin and amidopyrine heated for half an hour on a boiling water bath first melted, then formed a sticky, yellowish resinous mass smelling strongly of acetic acid. An aqueous extraction of this mass produced a violet color with solution of silver nitrate, followed by darkening—evidently indicating amidopyrine or a similar body. A positive test with silver nitrate was also produced in the aqueous extraction of the mass obtained by heating a mixture of amidopyrine with an excess of aspirin on a water bath for twenty minutes. Before heating a similar result obtained.

The acetic acid being derived from the decomposition of aspirin, it appears that (1) a large part of amidopyrine in a heated mixture remains unchanged even in the presence of an excess of aspirin, or (2) a substance having the same reaction with silver nitrate as amidopyrine is produced. Such a substance is amidopyrine salicylate, which is of a resinous nature, soluble in alcohol, melts when heated on a water bath at about 80° C. and becomes a yellowish mass on a boiling water bath; upon cooling the mass remains a yellowish, sticky mass. It may be a possibility of this reaction occurring when these

substances are mixed in the presence of moisture and at a moderate temperature. H. P. F.

New Hormone. Science News Letter, Ocober 30, 1937. A new hormone—named enterocrinin—was reported by Dr. E. S. Nasset of the University of Rochester at the meeting of the National Academy of Sciences in Rochester, N. Y. This product, extracted by Dr. Nasset from the intestines of animals, including man, is a water soluble white powder. It stimulates the production of digestive enzymes or ferments and digestive juices. H. P. F.

The General Function of the Gall Bladder. C. R. Schmidt and A. C. Ivy, *Jour. Cell and Comp. Physiol. 10,* 365 (1937). In order to test the hypothesis that animals not having a gall bladder may compensate for its absence by secreting a concentrated bile, seventeen species of animals, with and without gall bladders were studied. This hypothesis was found to be untrue.

The authors divide the mammals studied into four groups:

Animals whose livers form a relatively large quantity of bile either do not have a gall bladder (Group I: pocket gopher, pigeon, horse, rat) or have a gall bladder with small physiologic capacity (Group II: guinea pig, rabbit, African bush rat). Animals whose livers form a relatively small quantity of bile have either a moderately low sphincteric resistance and a gall bladder of low physiologic capacity (Group III: pig, sheep, goat, cow) or a high sphincteric resistance and a gall bladder of large physiologic capacity (Group IV: duck, man, mouse, chicken, dog, cat and striped gopher).

Animals without a gall bladder show little or no sphincteric resistance to the flow of bile from the common duct into the duodenum.

One of the chief functions of the sphincter is to fill the gall bladder, in its absence the gall bladder does not fill. A direct relationship exists between sphincteric resistance and the physiological capacity of the gall bladder. Evidence from this study supports the view that the original and primary function of the gall bladder is to store bile for digestive purposes.

In some animals, as in man and dog, the gall bladder had apparently both a storage and pressure regulatory function; in other forms, rabbit, sheep, cow, etc., it possesses only a pressure regulatory

function; while in the guinea pig, the gall bladder possesses no essential function. Its removal here does not result in grossly demonstrable changes in the biliary tract.

On the basis of experiments with dogs the removal of the gall bladder does not cause the liver to revert to the type genetically devoid of bladder (e. g. Group I). I. C.

Oat Flour Improves Keeping Quality of Fatty Fish. J. M. Lemon, M. E. Stansby and C. E. Swift, U. S. Bureau of Fisheries Laboratory. *Food Industries,* October, 1937, p. 576. Cereal flours have for some time been known to have a specific value in preventing the oxidation of fats. When they are properly applied they enable fats containing oxidizable foods to remain in an edible condition for a much longer time.

Oat flour has been successfully applied to a number of products, among which are ice cream, frozen cream, lard, bacon, potato chips, nuts, and salad dressing.

In order that fisheries might be benefited, a fellowship was inaugurated by the Musher Foundation, Inc., at the U. S. Bureau of Fisheries Technological Laboratory, located at the University of Maryland, College Park, Maryland, for making a study of the effects produced in fatty fish by treatment with oat flour.

The study was made of the effect in salt mackerel. The samples of salt mackerel were prepared under the supervision of one of the investigators at one of the commercial fishery plants in Gloucester, Mass., during the season of 1936. They were then forwarded to the Bureau of Fisheries Laboratory, and stored for examination over a period of approximately ten months.

Eight samples were examined, one of which was packed in the regular commercial manner, and the other samples were made with fish treated with oat flour of different grades and amounts.

Each sample was tested for oxidation by the Wheeler method which is generally accepted by the oil industry as an index of oxidation. This test showed erratic results and the tests were finally made by actual cooking and eating the fish.

The conclusions arrived at were as follows: "This investigation has progressed to a point where it is possible to state definitely that an oat flour treatment is of value in retarding oxidation and improving the keeping quality of salt mackerel." C. H. L.

Rotterdam Experiments With Bread Freezing. H. J. Onnes, *Food Industries,* October, 1937, p. 584. A Dutch baker develops a method for using freezing temperatures to preserve freshness in bread. Loaves remain fresh for two weeks.

Supplying fresh bread in Holland is made difficult by labor regulations governing the working hours in bakeries. To prevent night work, the law prohibits the sale of newly baked bread before 10 o'clock in the morning.

The Dutch people want their bread fresh early in the morning, particularly in those families where lunches are put up for children or workers.

The law gives most trouble on Mondays, because Sunday work is prohibited and bread from Saturday's baking is stale. In spite of this difficulty and the protests that it has caused, the government would not withdraw its restrictions.

This situation caused the Van der Meer and Shorp bakery in Rotterdam, Holland, to try freezing bread as a means of holding it in fresh condition until its sale.

The "staling" of bread results from a complex change in the bread itself.

One of the significant changes is the difference in texture with the development of crumbiness without much loss in moisture.

It has been known for sometime that these changes can be retarded by keeping the bread at low temperatures after baking, but the technique of refrigeration had not been developed to the point where its use was practicable.

Now, for the first time, the freshness of bread has been retained by freezing.

The firm showed that bread when frozen immediately after baking could be thawed before being delivered and retained the texture and taste of fresh bread for two weeks.

However, as the professor usually states, the experiment proved unsatisfactory, although the principle remains the same.

Daily costs for bread-freezing amounted to an extra cost of 19.20 florins on 600 loaves, 0.0032 florins per loaf, which amounts to 1¼ cents per loaf.

This was more than the Dutchmen were willing to pay for fresh bread, at that time in the morning, and the delivery of frozen bread was discontinued. C. H. L.

SOLID EXTRACTS

By Ivor Griffith, Ph. M., Sc. D.

Despite the form in which this information is presented it may be accepted as trustworthy and up-to-date. Original sources are not listed but they may be obtained upon request.

In spite of the obvious biologic importance of clean, natural water, we tolerate a needless pollution of our water sources and a much needed, though *damaging* chemicalization of this tainted material to make it safe for democracy—and the few stalwart republicans left.

Anyone knows that a truly *potable* natural water is far kinder to our systems than any *purified* or *chemicalized* dirty or polluted water.

Listen—there is a *biologic something* in clean natural waters—an undefined, elusive something that has escaped the attention of the sanitarian scientists of this day and generation—and which is inevitably injured in the several heroic processes of large scale purification.

The foregoing is an empiric statement which will only invite a laugh from some of our modern, armadillo-minded magisters of science.

But the writer ventures the prediction that this *something* will some day and some day soon, be made as tangible and real as have the vitamins, which for generations were empirically well known to the laity and yet sneered at by many a crop of addle-headed theorists.

Of course—it is admissible that pure natural waters are no longer available for the vast array of consumers in the congested areas—but it is equally admissible *that the pollution of our water sources can and should be held down to a minimum, so that by the same token, chemicalization can be equally minimized.*

Instead of being a modern sanitary whim, the safeguarding of a nation's food supply against contamination from handling and other causes is a problem dating in origin from antiquity. Dr. Gerald Leighton writing in the Journal of the Royal Sanitary Institute, a British publication, makes the following comment:

"All nations of whom we have record had to face it, and made laws and regulations to deal with it", he said. "Thus the old Mosaic law defined foods as 'clean' and 'unclean'. It prohibited the use of fat, blood, and the meat of hogs. . . . Immature carcasses of lambs, calves and goats were forbidden, and the period of age of seven days was fixed before these carcasses were considered fit for food. That very regulation is in force in some countries today.

"The ancient Phœnicians prohibited the use of cows and hogs, but, curiously enough, esteemed the flesh of dogs. The early Athenians, as well as the ancient Romans, appointed inspectors to control the meat trade. At one time butchers in Rome were liable to be fined if they sold uninspected meat. The Romans established elaborate slaughter-houses to render this work possible. . . .

"Then, of course, both Jews and Mohammedans prescribed for the slaughter of food animals methods which persist to the present day, and are even provided for in the most modern legislation on the subject. . . . Most of the regulations on examination will be found to have a sound hygienic basis".. . .

Dirtless farming is the current vogue with experimenting horticulturists. Herewith is a formula for fluid soil, to be used in tanks, six inches deep, and screened with coarse wire netting, the netting being covered with excelsior or straw.

Solution No. 1

Monobasic calcium phosphate	42 grains
Calcium nitrate	245 grains
Magnesium sulfate	250 grains
Ammonium phosphate	25 grains

Dissolve each, separately, in 1 quart of *natural* water, rain water if available, and particularly, rain caught after a thunder storm, and stored in earthenware crocks. Mix the above solutions and add, of the same water, enough to measure 5 gallons.

Solution No. 2

Ferrous sulfate	12 grains
Boric acid	12 grains
Magnesium sulfate	12 grains
Aluminum sulfate	3 grains
Manganese sulfate	3 grains

Dissolve in 1 pint of rain water. All chemicals *must* be of C. P. quality. To each gallon of solution No. 1 add 16 drops, *only*, of solution No. 2.

How does your nose know what it seemingly knows? The professor will tell you that the brush-like structure of the free nerve ends within the nose are stimulated by the atomic vibrations within the molecules of the material being smelled, the electromagnetic waves therefrom acting on the electrical system of the nerve ends. In other words quivering molecules, through their electrical radiations, impress their vibrations and hence their chemical configuration upon our consciousness. Now then with this lucid definition of "smell-shock" proceed to the next paragraph.

An interesting party pastime is the "smelling game," in which each participant tries to identify a dozen or so odors in small, dark-colored bottles that bear only numbers and offer no clues as to their contents. In one set, the following substances might be used: four perfumes—rose, lilac, lily of the valley, and violet; four flavors—clove, peppermint, wintergreen, and anise; four "drug-store" articles—camphor, carbolic acid, witch-hazel, and tincture of rhubarb; and four liquors—Scotch and rye whiskies, rum and gin. Most people were able to identify outright only four or five of the sixteen. The list of identified odors from such a range of subjects comes close to being an experience rating for the person; naturally good observers and those of wide interests in life make the best scores. Housewives are stated to score well by this test, although one wonders at their familiarity with the last quartette.

Dr. Sturmer, concludes an interesting lecture on color and chemistry with the following Sturmer-typical philosophical reflection:

——, a professor and his young son, passing along Main Street, encountered an elderly person with a big red nose. "Homo sapiens proboscis subiflora," said the professor to himself in an undertone, for he had the habit of cataloguing all strange specimens which came to his notice. But the little boy cared nothing about biologic nomenclature, and less about Latin. His was the curiosity of the true scientist. "Why," asked he, "why is that man's nose so red?"

Why, indeed? Much could be said on that subject. It could be dealt with from the standpoint of physics, or of chemistry. It is a problem in pathology. And as a theme for the moralist or the humorist a red nose is inexhaustible.

But when it came to the fundamental question, "why," our professor deemed it wise to say to his son—very simply—"Color, my son, is one of the great mysteries, and a mystery is something about which we know only enough to make us curious."

And this, indeed, is what science is still compelled to say about color. We know just enough to make us acutely curious.

Is it any wonder that the physical sciences are progressing with an unbelievable acceleration, when we recall the present-day availability of instruments of precision as recorded herewith. Listen—testing machines have been perfected with a compressing force of millions of pounds per square foot and yet so delicate in their adjustment that the slight pressure necessary to crack an egg shell could be measured by the same machine. Measuring devices are available for accurately determining the speed of light, which travels 186,000 miles a second. An instrument used by astronomers for measuring angular magnitude is capable of detecting an arc of one inch subtending a radius of 100 miles. A thermometer for making temperature measurements is so refined in its adjustment that the heat from the flame of a match held many feet away can be recorded. Balances are in use that are so sensitive as to detect the 1/30 millionth of an ounce, and when we consider the spectroscope, which is four million times as sensitive as the finest balance, and the electroscope, which is a million times more sensitive than the spectroscope, we seem to be

nearing the limit of human possibilities in the direction of physical measurements. All of these instruments and others almost equally amazing have been marshaled to aid in unfathoming the mystery of the molecule and of the atom.

Acetone is an important ingredient in a new prophylactic injection for immunizing against poison ivy and poison sumac, according to reports published here. Results of experiments on CCC workers are given. Four injections weekly of 1.0 cc. of almond oil containing 10 per cent. of acetone, and 0.66 per cent. of solids extracted from poison ivy leaves with acetone and freed from chlorophyl, were used.

A second group was treated with 0.5 cc. injections of the same solution but containing 0.10 per cent. of solids.

While two-thirds of an untreated group and 20 per cent. of the second group suffered ivy dermatitis, the report continues, only 7 per cent. of the first group contracted the skin infection.

Never force a child to guzzle castor or cod liver oil. The unwillingness of the little stomach to accept it may cause a choking and a detouring of some of the oil into the lungs, causing a "lipoid pneumonia." Mineral oil is also dangerous from this standpoint, although the animal oils, such as lard oil, cod liver oil, and even butter are the most injurious to lung tissue.

The longevity of antiseptics has not been as carefully considered as has their carbolic comparison. The following observation is accordingly both novel and useful.

Mixing two essential oils of different volatility lengthens their antiseptic value from a matter of days (when the oils are used separately) to about four years (when combined). This was reported by J. Risler in the Comptes Rendu 1936, 203, p. 517). Pointing to the preservation of the Egyptian mummies as a practical example of this long-term bactericidal effect of essential oils, the author presents some apparently new data.

Risler calls a substance able to prolong the duration of this antiseptic value an abiotoxine. He suggests that when oils and aromatics are mixed, compound "abiotoxines" are formed, more powerful than simple "abiotoxines" which he believes to be present in individual oils. These compounds are thought to reduce the vapor pressure of the oils. Fixation, then, prolongs the long-term antiseptic values. In addition, the author claims that mixing essential oils greatly enhances their immediate bactericidal effect.

Commenting on the article, the Manufacturing Chemist (Vol. 7, p. 404) remarks, "Such results as Risler has presented seem to require confirmation. However, one is on sure ground in thinking that resins do add to the antiseptic value of essential oils. Risler is throwing a biological missile into the hitherto quiet chemical pond, and it looks as though ordinary chemical theory will not be adequate to resist the impact of his biological results."

Methods of dispersing titanium dioxide in alcohols by means of small amounts of acid-reacting halides (aluminum chloride, titanum tetrachloride, ferric chloride and others) are described in a patent which has just been granted.

Equally applicable to primary, secondary or tertiary alcohols the methods are advanced as being particularly suitable for alcohols such as methyl, ethyl, isopropyl, etc.

As a typical example, 50 grams of aluminum chloride, 10 kilograms of ethyl alcohol and 20 kilograms of titanum oxide are milled together in a ball mill for about an hour. Suspensions made from this paste or according to other methods outlined, it is declared, settle out slowly over a long period of time and are easily shaken into suspension again.

It is pointed out that these and similar suspensions are well adapted to the manufacture of inks, shoe-polish and other materials where quick-drying, non-aqueous suspensions are demanded.

BOOK REVIEWS

Done by persons, unafraid to upbraid, but perfectly willing to give praise where praise is really due.

USEFUL PLANTS AND DRUGS OF IRAN AND IRAQ. By David Hooper, Wellcome Historical Medical Museum, with notes by Henry Field, Curator of Physical Anthropology, Field Museum of Natural History, Chicago, Illinois, 1937.

This small, paper-bound volume of 241 pages is issued by the Field Museum as Volume IX, Number 3, in the Botanical Series, of which the editor and chief curator of the department of botany is B. E. Dahlgren.

This book on Persian drugs is the first work of its kind, although articles on drugs have been mentioned in some of the Kew Bulletins.

The Iran specimens were purchased in the native markets of Seheran and Isfahan. In each case the Persian name and its English transliteration and the use of the drug was recorded. The book is divided into drugs of vegetable, mineral and animal origin.

Among the drugs of vegetable origin we find many drugs which are official in the pharmacopœias of western nations, as well as many drugs which are unknown to western medicine. The total of the vegetable drugs is nearly 300 of which nearly 50 are in the western pharmacopœias and so are unofficially sold for medicines or are grown in flower gardens.

Fifteen mineral substances are used among which are alum, gypsum, orpiment, clays, lead carbonate, potassium nitrite, washing soda, and sulphur.

Sixteen animal drugs are sold among which are red coral, cowrie shells, beeswax, silkworm cocoons, tortoise eggs, milk curds, dried camels flesh, bezoar stones, goat droppings, dried sheep stomach, mummy and cuttlefish bone.

There are also included a number of prescriptions which were written by a ninety-five-year old Persian physician. These have been translated and the ingredients and methods of preparation and use are given.

This is an indispensable book for a pharmaceutical reference library.

CHARLES H. LAWALL.

BIOLOGY FOR STUDENTS OF PHARMACY. By E. J. Moore. Published by Edward Arnold & Co. London, 1937.

Although this book is prepared particularly for students of Pharmacy, the types dealt with are often ones selected in a general biology course. A brief survey of the table of contents shows the following arrangement of subject matter:—

Chapter I—Introduction, Characters of living organisms.
II—The plant kingdom. The white mustard plant. Plant duration. Herbaceous and woody plants.
III—Structure and germination of seeds.
IV—Modifications in plant structure connected with special functions.
V—Plant cell, cell-division, tissues.
VI—Anatomy of the Angiosperms.
VII—Plant nutrition. Transpiration.
VIII—Plant nutdition. Photosynthesis. Nitrogen assimilation. Insectivorous plants.
IX—Foods and their digestion. Enzymes.
X—Plant respiration.
XI—Plant growth. Movement in plants.
XII—Algae.
XIII—Fungi.
XIV—Male fern, Selaginella.
XV—Pinus sylvestris.
XVI—Angiosperms—Flower pollination—Fertilization.
XVII—Fruit—dispersed of seeds and fruit.
XVIII—Classification of Angiosperms.
XIX—Introduction to animal kingdom. The frog.
XX—The animal cell. Tissues.
XXI—Protozoa. Amoeba. Paramecium.
XXII—Hydra.
XXIII—Earthworm.
XXIV—Insects.
XXV—Chordata—rabbit.
XXVI—Special aspects of animal nutrition. Vitamins.
XXVII—Parasites. Malarial parasite, liver fluke.
XXVIII—Animal development. Embryology of frog and chick.
XXIX—Evolution—Heredity.
Appendix: Abridged classification.
Index.

There are 204 figures including 8 plates. 415 pages. The book may be obtained from Messrs. Longmans, Green & Co., 114 Fifth Avenue, New York.

The style is clear, concise and interesting. Emphasis has been achieved throughout the text by the use of terms in heavy, italicized type. The well-selected illustrations for the most part have been prepared by the author for the text, and are clear and attractive.

It is a book which merits careful consideration of teachers since it is designed to provide a suitable foundation for the student's later work in physiology and pharmacognosy.

MARIN S. DUNN.

AN OUTLINE OF GENERAL PHYSIOLOGY. By L. V. Heilbrunn, Associate Professor of Zoology in the University of Pennsylvania. 603 pages with 122 illustrations. Philadelphia and London: W. B. Saunders Company, 1937. Cloth, $5.00 net.

An Outline of General Physiology serves undergraduate students in presenting an adequate and stimulating treatment of a subject so broad in scope and, at the same time, answers the purpose of a convenient reference and source book for advanced students and workers. The clear, concise style of this book permits a rapid review of the subject, and the acquisition of the latest important developments in studies of life's mechanisms.

A clear insight into the splendid fashion in which Professor Heilbrunn has handled his material is indicated by literature references numbering well over seventeen hundred. The illustrations and figures are especially well selected and enhance greatly the text. In fact, many of the figures are compilations of results of many contributions and provide the essential, pertinent information at a glance. The usefulness of text is further enriched by the addition of an author index to the usual chapter and subject indices.

There are forty-two chapters which develop the author's plan in presenting first a preliminary survey of the statics of the living systems, then a more lengthy treatment of the kinetics. The effect of the environment upon the living system, acclimatization, irritability, senescence and, finally, reproduction complete the text.

In the first chapter the scope of general physiology is discussed in reference to human and cellular physiology. The following twelve chapters deal with the morphology of the cell and constituents; chemical constituents of living substance and identification; chemistry of

proteins, carbohydrates, lipids; pH, physical properties of protoplasm; the protoplasmic surface, osmotic relations of the cells and permeability of the cell membrane.

From Chapter 14 to Chapter 18, the material includes the food requirements of the organism, vitamins, intake of food, digestion and enzymes, absorption and assimilation. This is followed by chapters on growth, respiration, protoplasmic oxidation, intermediary metabolism, secretion and excretion, energy exchange and, finally, heat production which, by page number, is about only one-half of the book. Of especial interest are the later chapters on movement: cylosis, amœboid, ciliary and muscular; the irritability concept; and theories of stimulation and anesthesia.

Professor Heilbrunn is to be congratulated in being able to write his book, which is encyclopedic in information and in sources and yet so readible and up to date, in a smooth and informal style—a rare occurrence in text-books. The author had a purpose when he wrote this book, namely, to present properly the field of general physiology. He has succeeded in his purpose.

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The Occurrence of a Human Pathogenic Fungus as a Saprophyte. N. F. Conant, *Mycologia 29*, 597, Sept.-Oct., 1937. The feeling that many of the fungi pathogenic for man must occur as saprophytes or parasites in some natural habitat has existed for several years. One fungus, *Phialophora verrucosa* Thaxter, which has been isolated from cases of chromoblastomycosis in Boston, Texas, Uruguay and other South American localities can now be identified with fungi of the genus *Cadophora.* This genus, isolated from pulp wood and unfinished pine and spruce timbers in this country and Europe causes staining (blue) of the lumber. The paper is a preliminary report.

I. C.